UNIVERSITÀ DEGLI STUDI DI TORINO

Title: Should we SHIFT our thinking about digoxin?

Observations on ivabradine and heart rate reduction in heart failure

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Abstract

The importance of heart rate in the pathophysiology of heart failure with reduced LVEF has recently attracted attention. In particular, the findings of the Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial (SHIFT), have put special emphasis on heart rate reduction with ivabradine for improvement in clinical outcomes. Of course there is a much older drug that reduces heart rate i.e. digoxin. In this short commentary we retrospectively analyse the Digitalis Investigation Group (DIG) Trial looking at the primary composite endpoint used in SHIFT (i.e. cardiovascular death or hospital admission for worsening heart failure) and compare the effect of digoxin on this endpoint with that of ivabradine. A remarkably similar risk reduction in the composite outcome and in its components appears evident amongst patients receiving the active treatment in both studies (although ivabradine was added to a beta-blocker whereas digoxin was not). This raises the question of whether the Cardiological community dismissed digoxin too readily and if we should reappraise its potential role in the treatment of heart failure.

Key Words

Heart failure

Heart rate

Digoxin

Ivabradine

Left ventricular ejection fraction

The key characteristics of the patients enrolled in the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT) and the Digitalis Investigation Group trial (DIG) trials are shown in Table 1. The remarkable similarity between the results of these 2 trials (Table 2) is a reminder that, in addition to beta-blockers and ivabradine, there is another treatment for heart failure which reduces heart rate i.e. digoxin.[1,2]

Because it did not reduce mortality and perhaps because it was not promoted, digoxin has not been seen as a useful treatment for patients with systolic heart failure in sinus rhythm over recent years.[3] Contemporaneous trials showing large benefits of spironolactone in patients with severe heart failure and similarly impressive benefits of beta-blockers across the whole spectrum of symptom severity eclipsed the findings of DIG. [4,5-7]

Endpoints in DIG and SHIFT

DIG was also performed at a time when all-cause mortality was perceived to be the most appropriate end-point for trials in systolic heart failure. More recently the importance of morbidity, principally heart failure hospitalization, has been recognized and it is also now accepted that heart failure interventions are unlikely to reduce non-cardiovascular death.[8] Consequently, the composite morbidity-mortality outcome of cardiovascular death or hospitalization for heart failure has become the most commonly used endpoint in recent heart failure trials, including SHIFT.[2,9,10] Re-analysis of DIG shows that digoxin led to a highly significant 15 (9-21)% relative risk reduction in this composite outcome as compared with an 18 (10-25)% relative risk reduction in SHIFT, both $p<0.001$ (Figure 1 and Table 2). In both trials the primary effect was on heart failure hospitalization without any significant effect on

cardiovascular death. Heart failure hospitalization was reduced by 26 (17-34) % with ivabradine and by 28 (21-34) % with digoxin (both $p<0.001$). Further inspection of the two trials shows very similar effects of digoxin on the other outcomes reported by the SHIFT investigators. Notably, both drugs reduced the proportion of patients admitted to hospital for any reason (Table 2).

Ivabradine and heart rate reduction

An entry criterion for SHIFT was a heart rate ≥ 70 beats per minute.[2] As a consequence, the mean baseline heart rate was 80 beats per minute. Compared with placebo, ivabradine reduced heart rate by 11 beats per minute at 28 days and 9 beats per minute at 1 year, a greater reduction in heart rate than achieved with digoxin (see below). An earlier trial, morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction (BEAUTIFUL), required patients to have a heart rate entry of at least 60 beats per minute.[11] The mean baseline heart rate in BEAUTIFUL was 72 beats per minute and the placebo-corrected reduction in heart rate was 7 beats per minute at 6 months and 6 beats per minute at 12 months. This latter finding is consistent with the observation that the heart rate reduction with ivabradine is greater in patients with a higher starting heart rate.[2,12] In both trials, the reduction in heart rate was achieved despite the use of background beta-blocker therapy (although not always in a recommended dose[13]).

Digoxin and heart rate reduction in sinus rhythm

The baseline heart rate in DIG was 78 beats per minute. The use of beta-blockers was not recorded but was likely to have been very infrequent. Although change in heart rate was not reported in DIG, prior studies reported the effect of digoxin in patients

with heart failure in sinus rhythm. The largest study to do so was the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme trial (RADIANCE), although this was a trial of digoxin withdrawal.[14] Compared with continuation of digoxin, withdrawal of digoxin in RADIANCE led to a significant increase in heart rate of 7 beats per minute over 3 months from a baseline of 77 per minute. Two smaller placebo-controlled cross-over studies showed significant reductions in heart rate of 5 to 6 beats per minute.[15,16]

The Dutch Ibopamine Multicenter Trial (DIMT) investigators carried out ambulatory ECG monitoring in a subset of 50 patients receiving no background heart failure therapy.[17] These patients were randomized to placebo, ibopamine or digoxin. Mean heart rate over 24 hours did not change from baseline in the placebo or ibopamine group but was reduced from 78 ± 7 to 74 ± 8 beats per minute in the digoxin group ($p=0.005$).

Digoxin is thought to reduce heart rate mainly by enhancing activity of the parasympathetic nervous system although it probably also inhibits the sympathetic nervous system as it lowers plasma norepinephrine levels.[18-21] The vagal actions of digoxin also enhance heart-rate variability, an effect that is obtained even with low doses.[22-24] In contrast to ivabradine, the addition of digoxin to a beta-blocker has not been studied in patients with systolic heart failure in sinus rhythm. As some of the heart rate reducing action of digoxin is due to an anti-sympathetic effect, concomitant beta-blockade may attenuate the bradycardic response to digoxin. However it is unlikely that beta-blocker treatment will eliminate the heart rate lowering action of digoxin which is probably mainly vagally driven.[19] Certainly, the combination of digoxin and a beta-blocker gives greater heart rate reduction than either drug alone in

patients with atrial fibrillation, which is a frequent co-morbidity in patients with heart failure (and in which ivabradine is ineffective).[25,26]

Left ventricular ejection fraction (LVEF)

As ivabradine's only known effect is to reduce heart rate, it was surprising that its use in SHIFT led to a placebo-corrected increase in LVEF of 2.7% ($p<0.001$).[27] The placebo-corrected change in BEAUTIFUL (in which the reduction in heart rate was less) was smaller 1.6% ($p=0.009$).[28] Two of the larger controlled trials with digoxin showed a placebo-corrected change in LVEF of 3.5% over 6 months ($p<0.001$) and 3.7% over 3 months ($p<0.01$), respectively.[29,30] Although it has long been assumed that the increase in LVEF with digoxin is due an inotropic action of the drug, the findings of SHIFT raise the possibility that some of this effect of digoxin may be related to heart rate reduction (although the increase in LVEF with digoxin was somewhat greater than in SHIFT despite smaller reductions in heart rate).

Perspective

The recent finding that lowering heart rate with ivabradine reduces the risk of hospitalization for worsening heart failure should make us revisit the role of digoxin in the management of heart failure. Although probably not as potently bradycardic as ivabradine, digoxin also improves heart rate variability and seems to increase LVEF to a greater degree. The benefit of digoxin was demonstrated across the full range of heart rates in DIG, although patients in DIG were not treated with a beta-blocker. Conversely, in SHIFT, the benefit of ivabradine was shown only in patients with a persistently high heart rate, although most patients in that trial were on a beta-blocker. Indeed there was a significant interaction between baseline heart rate and the effect of

ivabradine in SHIFT, whereby there was a greater benefit of treatment in patients with a heart rate of ≥77 beats per minute.[2] Interestingly, a recent study has shown patients with a persistently high heart rate constitute a small minority of adequately beta-blocked patients.[31] Digoxin is, of course, of value in patients with atrial fibrillation whereas ivabradine does not work in these patients. On the other hand, the toxicity of digoxin is well recognized and it also has interactions with many other drugs. Combination with a beta-blocker has the potential to cause atrioventricular block in particular, although more than half of patients in the pivotal beta-blocker trials were receiving background digoxin therapy and this problem was reported infrequently.[5-7] Perhaps the findings of SHIFT, together with our retrospective hypothesis-generating analysis of DIG, should make us concerned that we dismissed digoxin too readily and that we should reconsider whether this inexpensive and generally well tolerated and safe agent still has a role to play as a treatment for heart failure? It is worth reflecting that in DIG there were 8 fewer patients admitted and 18 fewer admissions per 100 patients treated with digoxin compared with placebo. In other words, treatment of 13 patients for 3 years prevented 1 patient being admitted at least once with worsening heart failure i.e. the number needed to treat (NNT) for 3 years was only 13. For patients in sinus rhythm, the treatment algorithms in current guidelines recommend digoxin almost as a "last resort" in patients who remain significantly symptomatic despite everything else – maybe we should reconsider this?[3]

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FIGURE LEGEND.

Figure 1. Kaplan-Meier cumulative event curves for the composite outcome of cardiovascular death or heart failure hospitalization in the Digitalis Investigation Group trial (DIG) [A] and the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT) [B*].

* Adapted from Lancet 2010; 376: 875-85.

Table 1. Baseline characteristics of the patients enrolled in the Digitalis Investigation Group trial (DIG) and in the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT).

	SHIFT n=6505	**DIG n=6800**
Age (years)	60	64
Sex (male)	76%	78%
Ethnic origin		
White	89%	85%
Nonwhite	11%	15%
BMI	28	27
Heart rate	80	79
SBP	122	126
LVEF	29%	28%
eGFR	75	64
NYHA		
Class I	-	13%
Class II	49%	54%
Class III	49%	31%
Class IV	2%	2%
Primary cause of HF		
Ischaemic	68%	71%
Non-ischaemic	32%	29%
Prior myocardial infarction	56%	65%
Hypertension	66%	45%
Diabetes	30%	28%
Beta-blocker	89%	N/A
Ace-inhibitor	79%	94%
ARB	14%	0
Diuretic	83%	82%
Antialdosterone agents	60%	N/A*
Cardiac glycosides	22%	N/A

ICD	3%	0
CRT	1%	0

* Potassium sparing diuretic = 8%

Table 2: Clinical outcomes in the Digitalis Investigation Group trial (DIG) and the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT).

	SHIFT				**DIG**			
Outcome	**Ivabradine (n=3241)** n (%)	**Placebo (n=3264)** n (%)	***HR (95% CI)***	**P value**	**Digoxin (n=3397)** n (%)	**Placebo (n=3403)** n (%)	***HR (95% CI)***	**P value**
Primary composite outcome in SHIFT								
Cardiovascular death or heart failure hospitalization	793 (24)	937 (29)	*0.82 (0.75,0.90)*	<0.001	1501 (44)	1653 (49)	*0.85 (0.79,0.91)*	<0.001
Hospitalization								
Heart failure hospitalization	514 (16)	672 (21)	*0.74 (0.66,0.83)*	<0.001	910 (27)	1180 (35)	*0.72 (0.66,0.79)*	<0.001
Cardiovascular hospitalization	977 (30)	1122 (34)	*0.85 (0.78,0.92)*	<0.001	1694 (50)	1850 (54)	*0.87 (0.81,0.93)*	<0.001
All-cause hospitalization	1231 (38)	1356 (42)	*0.89 (0.82,0.96)*	<0.01	2184 (64)	2282 (67)	*0.92 (0.87,0.98)*	<0.01
Deaths								
Heart failure death	113 (3)	151 (5)	*0.74 (0.58,0.94)*	0.01	394 (12)	449 (13)	*0.88 (0.77,1.01)*	0.06
Cardiovascular death	449 (14)	491 (15)	*0.91 (0.80,1.03)*	0.13	1016 (30)	1004 (30)	*1.01 (0.93,1.10)*	0.78
All-cause death	503 (16)	552 (17)	*0.90 (0.80,1.02)*	0.09	1181 (35)	1194 (35)	*0.99 (0.91,1.07)*	0.80

HR = hazard ratio CI = confidence interval

Figure 1: Kaplan-Meier cumulative event curves for the composite outcome of cardiovascular death or heart failure hospitalization in the Digitalis Investigation Group trial (DIG) [A] and the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT) [B*]. * Adapted from Lancet 2010; 376: 875-85.

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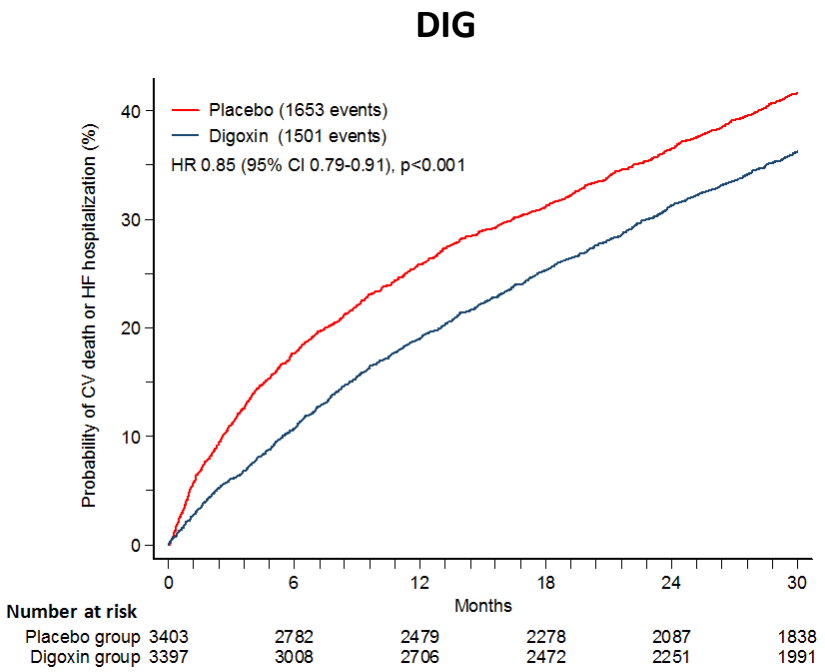

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